IN THE UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
HUNTINGTON DIVISION

CLAUDE R. KNIGHT AND CLAUDIA STEVENS, INDIVIDUALLY AND AS PERSONAL REPRESENTATIVES OF THE ESTATE OF BETTY ERELENE KNIGHT, DECEASED	)	
Plaintiffs,	)	Civil Action No. 3:15-cv-06424
v.	)	JURY TRIAL DEMANDED
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.	)	
Defendant.	)	

DEFENDANT'S MOTION IN LIMINE NO. 7
TO EXCLUDE THE OPINIONS OF DR. BRIAN HARVEY

Boehringer Ingelheim Pharmaceuticals Inc. ("BI") moves to exclude the opinions of Plaintiffs' regulatory expert, Brian Harvey, M.D. The following opinions are inadmissible:

- Opinions regarding the 110 dose of Pradaxa, which are irrelevant and preempted.
- Opinions regarding monitoring, which are unreliable and do not fit the facts of this case.
- "Reasonable company" opinions, which have no basis and specifically ignore the actual conduct of other pharmaceutical companies.
- Opinions on cherry-picked BI company documents, which are not proper expert testimony.
- Opinions regarding Praxbind, which are irrelevant here.
- Foreign labeling opinions.

The deposition record justifies precluding these opinions, but in the event that there is any question regarding admission, BI respectfully requests an evidentiary hearing on this motion.

FACTS

Plaintiffs seek to offer Dr. Brian Harvey to testify on a range of matters, including BI's conduct, the Pradaxa labeling, the reversal agent, and monitoring. Dr. Harvey is a former FDA employee whose tenure was marked by a United States Senator's calling for an Inspector General investigation into his conduct. *See* Ex. A, Harvey 11/30/17 Dep. at 47:14-48:19. After leaving the FDA, Dr. Harvey worked for two different pharmaceutical companies, including Pfizer, which makes a competitor product to Pradaxa, Eliquis. *Id.* at 45:9-15, 53:23-54:12, 56:14-57:4. Even though many of Dr. Harvey's Pradaxa criticisms plainly apply to this competitor product, he claimed an inability to answer questions about his prior company's work, admitting that he would need to "talk to Pfizer to make sure [he] wasn't violating any agreement" before answering questions about Eliquis. *Id.* at 72:22-73:6; *see also id.* at 67:21-69:4 (declining to answer questions about Eliquis, even after acknowledging seeing literature discussing monitoring for *all* novel oral anticoagulants ("NOACs"), and having referenced a presentation discussing whether monitoring should be required for Eliquis and other NOACs).

Although Dr. Harvey hinges his expertise on his prior work at the FDA, he could not affirmatively state that he reviewed the full regulatory or scientific record regarding Pradaxa. *See, e.g.*, *id.* at 97:23-98:14, 134:4-11, 149:3-16, 322:23-323:18. Indeed, as noted below, he made clear throughout his deposition that broad swathes of his opinions were unsupported by a complete record review and based on nothing more than his say-so.

LEGAL STANDARD

Under Rule 702, expert testimony is admissible if it will "help the trier of fact to understand the evidence or to determine a fact in issue" and (1) is "based upon sufficient facts or data" and (2) is "the product of reliable principles and methods" which (3) has been reliably

applied "to the facts of the case." Fed. R. Evid. 702. Evidence is admitted if it "rests on a reliable foundation and is relevant." *Daubert v. Merrell Dow Pharm.*, 509 U.S. 579, 597 (1993). The proponent of the expert must "come forward with evidence from which the court can determine that the proffered testimony is properly admissible." *Md. Cas. Co. v. Therm–O–Disc, Inc.*, 137 F.3d 780, 783 (4th Cir. 1998).

ARGUMENT

I. Dr. Harvey's Opinions About Other Doses of Pradaxa Are Inadmissible.

As explained in BI's Motion in Limine No. 3, Ms. Knight was prescribed the 75 mg dose of Pradaxa, and there is no claim by any expert that she should have been prescribed a 110 mg dose. Further, claims related to that dose are preempted. Accordingly, any claim arising from the 110 mg is irrelevant and does not fit this case. *See Edwards v. Ethicon, Inc.*, No. 2:12-CV-09972, 2014 WL 3361923, at *2 (S.D.W. Va. July 8, 2014) (quoting *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 591–92 (1993)) ("'Expert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful.'"); *Wise v. C.R. Bard, Inc.*, No. 2:12-CV-1378, 2015 WL 521202, at *8 (S.D.W. Va. Feb. 7, 2015); (excluding expert testimony regarding degradation where "there does not appear to be any connection between [the expert's] surface degradation opinions and Ms. Wise specifically").

II. Dr. Harvey's Monitoring Opinions Should Be Excluded.

Dr. Harvey's monitoring opinions are unreliable and irrelevant.

As an initial matter, Dr. Harvey readily admitted during his deposition to his lack of qualifications to offer such opinions, conceding that he is not a hematologist, pharmacologist, pharmacokineticist, or expert in modeling. Harvey 11/30/17 Dep. at 82:5-6, 82:18-21, 112:21-22.

Moreover, the monitoring opinions do not fit the facts of this case because there is no showing monitoring would have altered the outcome here. As explained in BI's motion to exclude Dr. Ashhab's testimony, there is no reliable testimony regarding what Ms. Knight's plasma concentration levels would have been while she was taking Pradaxa. For this reason alone, the monitoring opinions should be excluded.

In addition, Dr. Harvey's opinions are unreliable.

Dr. Harvey was initially unwilling to offer a target blood range, instead stating that BI should arbitrarily select one of the many inconsistent target ranges reflected in the documents he selectively cites in his report. But Dr. Harvey directly contradicted this opinion by acknowledging that there is no single target range for all patients, before contradicting himself yet again by proposing for the first time a subjective, unsupported target range applicable to all patients. Dr. Harvey also separately proposed monitoring recommendations for certain "high-risk" patient groups, he articulated these opinions for the first time during his deposition and without defining adequate support.

As to whether there is an optimal target range for all patients, Dr. Harvey offered a series of contradictory and conflicting opinions. Initially, despite citing numerous potential therapeutic ranges in his report and during his deposition, Dr. Harvey declined to identify a specific target range that should be included in the Pradaxa label. Instead, Dr. Harvey simply cherry-picked an array of theoretical potential ranges in his report, and then sought to criticize BI for not identifying any one of these inconsistent ranges. *See* Ex. A, Harvey 11/30/17 Dep. at 168:23-169:20 (identifying three separate potential ranges or cut-offs: "I agree with what I saw in Dr. Temple's slides where he talked about 50 to 150. I could certainly understand if you wanted to have a cutoff of 200, I think, or 75 to 150 is another range."); *id.* at 170:4-8 (identifying 50 to 150

ng/ml and 75 to 150 ng/ml as potential ranges, without differentiating between the two ranges); *id.* at 187:15-188:4 (identifying 40 to 200 ng/ml as another potential range); *id.* at 170:22-171:16, 175:5-13 (identifying the 10th to 90th percentiles of plasma concentrations seen in RE-LY as another potential range, but admitting that he did not know what these specific values were, and acknowledging that these percentiles are arbitrary points along the data spectrum). But these opinions, taken alone, are inherently contradictory, as Dr. Harvey's inability to identify a specific target range for Pradaxa invalidates his theory that BI should have warned of the need to monitor and maintain patients within a specific range.

At the same time, Dr. Harvey undermined this testimony by disclaiming that any target range existed for all patients, instead readily conceding that "***there is no single plasma concentration range that provides optimal benefit/risk for all patients***." *Id.* at 195:25-196:8 (emphasis added); *see id.* at 195:21-22 ("[Y]es, it's a true statement for all patients, there's no single range . . . ."). Then, later in the same deposition, Dr. Harvey again contradicted himself by offering his opinion -- for the first time -- that there *is* a single range for all patients, that this range is 50 to 150 ng/ml, and that patients should be monitored to maintain plasma levels within this range. *Id.* at 228:17-21, 232:13-233:3. But this view cannot be reconciled with Harvey's prior testimony. Nor is this opinion consistent with those offered by Plaintiffs' other experts or the consensus views of the scientific and regulatory community worldwide. *See, e.g., id.* at 233:4-12.

In addition to his conflicting opinions as to whether a target range exists for all patients, Dr. Harvey also articulated -- again, for the first time during his deposition -- a similarly unsupported view that certain "high-risk" patients should be monitored and maintained within specific target ranges. But as to one of the potential "high-risk" groups he proposed -- patients age 75 years and older -- Dr. Harvey stated only that such elderly patients should be maintained in a target range of

50 to 150 ng/ml, *id.* at 211:18-212:3; given that this is the same range that he also claimed should apply to all patients, his rationale for providing separate (duplicative) guidance for this elderly population is unclear. With respect to another "high-risk" group he identified -- patients with a previous GI bleed or other bleeding -- Dr. Harvey offered only that the target range "might be 50 to 100" ng/ml. *Id.* at 219:3-7. And as to the other two "high-risk" groups he proposed -- patients with some unidentified level of impaired renal function, and patients taking some unspecified list of co-medications -- Dr. Harvey could not articulate specific target ranges or even define with any particularity how those patients might be identified, declining to elaborate on these critical issues and instead repeatedly deferring to others.[1]

In terms of how such a monitoring regimen might be implemented, Dr. Harvey disclaimed any opinion as to how often monitoring should be done. *Id.* at 285:23-286:2. He could not provide specific recommendation as to how often patients should be tested as they age or based on renal function. *See id.* at 229:18-230:4, 230:13-19. And he could not say how long after taking the medicine that patients should be tested, declining to offer a specific opinion on the appropriate time for testing and instead deferring to a pharmacologist. *Id.* at 244:12-245:16.

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[1] *See* Ex. A, Harvey 11/30/17 Dep. at 213:4-11 (testifying as to renal function that "I would not make a specific recommendation. I would recommend that it would be based upon kidney function and then leave the specifics to the renal experts"); *id.* at 216:22-25 ("Q. . . . Do you have a specific renal function level at which you would recommend testing blood concentration levels to hit a target range? A. No, I don't."); *id.* at 224:15-24, 225:10-15 (deferring to others on specific target range for patients with impaired renal function, and deferring to other on specific creatinine clearance level to identify patients with impaired renal function); *id.* at 216:18-20 ("Making specific recommendations on renal ranges is not part of the purview of what I did as a regulatory consultant."); *id.* at 220:18-22 (testifying that he does not "have a comprehensive list" of co-medications, and identifying only verapamil as a potential co-medication); *id.* at 221:21-23 (declining to offer any opinion as to the target range for patients on verapamil, and instead deferring to others); *id.* at 221:14-20 (failing to identify any other co-medications).

Critically, Dr. Harvey does not understand the data that form the foundation for his opinions regarding monitoring, and he therefore cannot assist the jury in drawing conclusions in this case. Although Dr. Harvey's proposed target ranges are derived in part from BI's and the FDA's pharmacokinetic modeling to predict the theoretical stroke benefit and bleed risk corresponding to specific blood concentrations, Dr. Harvey made clear during his deposition that he lacked a sufficient understanding of this modeling to explain his methodology in a form useful to the jury. In particular, Dr. Harvey admitted that he had never performed any pharmacokinetic modeling and could not replicate BI's modeling himself, *id.* at 83:10-13, 335:22-336:2; that he did not know what variables BI controlled for in conducting the modeling, *id.* at 336:3-5; that he did not know whether the patient data used in the modeling was representative of the overall patient data set, despite acknowledging that this was an "important fact," *id.* at 336:6-14, 349:23-350:12; and that he "wouldn't be able to tell" how accurate the model was when compared to what was seen in the real world, *id.* at 343:12-18.

Further, despite relying in part on an exposure-response graph published as Figure 2 in the Reilly paper as a basis for his monitoring opinion,[2] Dr. Harvey did not understand whether that graph was based on actual patient data or modeled data, *id.* at 200:25-201:10; although the stroke and bleeding event probabilities reflected in the graph were specifically calculated for a 72-year-old male, he could not say how these probabilities would differ for patients with other characteristics, *id.* at 202:10-20; and he did not understand the predictive value analysis published in the same paper, comparing what was predicted in the model and real world data, *id.* at 340:16-342:14. Similarly, although he cited target ranges from a pediatric clinical trial for

[2] *See, e.g.*, Ex. A, Harvey 11/30/17 Dep. at 69:10-15, 179:22-180:4; *see also* Ex. B, Reilly et al., *The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients*, 63 J. Am. C. Cardiology 321, 326 (2014) (Fig. 2).

Pradaxa to support his monitoring opinion, Dr. Harvey acknowledged that that he did not understand the details of how modeling was used in connection with dosing in that trial. *Id.* at 112:24-114:3.

Indeed, Dr. Harvey repeatedly emphasized that he had no expertise in modeling and did not understand the details of the modeling underlying his opinions. *See id.* at 112:21-22 ("I think we've already established that I'm not an expert in modeling."); *id.* at 113:25-114:3 ("Not being an expert in that area, which, we've already established, I don't know the specific details."); *id.* at 332:20-21 ("I think we've established I'm not an expert on modeling."). When an expert does not understand the data he uses, he necessarily employs an unreliable methodology.

Further, Dr. Harvey's monitoring opinions rely entirely on his own subjective judgment. Dr. Harvey's proposed plasma concentration ranges and identification of "high-risk" populations depend on his arbitrarily concluding that, above a specific threshold for a particular patient, the additional stroke protection is not significant enough to offset the corresponding increased bleeding risk. But Dr. Harvey undermined this opinion by agreeing that stroke protection benefit increases even past 200 ng/ml -- a value well beyond the target range he proposed. *See id.* at 185:7-11.

In addition to relying on his subjective weighing of stroke and bleed risk, Dr. Harvey admitted that his arbitrary opinions regarding "high-risk" patients are not based on any actual data. *See id.* at 169:10-20. Indeed, Dr. Harvey acknowledged that, before implementing any testing and dose adjustment scheme like the one he proposed, he would want to be sure that it would actually lead to safer results and not cause patient harm -- but that he was unaware of any actual data supporting his proposed approach. *Id.* at 278:4-19. Ultimately, Dr. Harvey's opinion boils down to his subjective belief "that there are still unanswered questions and they need to be

addressed by clinical data, and that data will then answer or address the questions that I have raised." *Id.* at 291:21-25. But subjective opinions offered without any clear methodology or standards do not constitute reliable scientific evidence. Separately, given the lack of data demonstrating that dose adjustments improve outcomes, Dr. Harvey cannot show that his opinions have a reasonable error rate.

Dr. Harvey's monitoring opinions (with the exception of his admissions that routine monitoring should not be required[3] and that there is no optimal range[4]) also conflict with the consensus of the scientific and regulatory communities, which endorse BI's conclusion that "[t]here is no single plasma concentration range that provides optimal benefit-risk for all patients"[5] and that monitoring and dose adjustment should not be required. Dr. Harvey agreed that many scientists -- both inside and outside BI -- have advanced the view that monitoring is not required. *Id.* at 439:14-19. He could not point to a single BI employee whose ultimate opinion, based on the data, was that monitoring is appropriate. *Id.* at 462:18-22. He conceded that his opinion regarding a one-time initial blood measurement is inconsistent with published data, and could not cite any data to the contrary. *Id.* at 247:18-248:5, 250:25-251:14. Ultimately, Dr. Harvey's testimony confirmed that the consensus view of the scientific and regulatory

[3] *See* Ex. A, Harvey 11/30/17 Dep. at 12:12-21 (testifying that "I don't believe that routine monitoring is the answer"); *id.* at 15:15-19 (agreeing with the FDA's approval of the 150 mg dose of Pradaxa "[w]ith no blood monitoring requirement"); *id.* at 314:13-24 (agreeing with the statement in the Pradaxa European label that "Pradaxa does not in general require routine anticoagulant monitoring"); *id.* at 360:16-25 (agreeing with the European Medicines Agency's conclusion that "routine therapeutic drug monitoring of Pradaxa should not be recommended").

[4] *See* Ex. A, Harvey 11/30/17 Dep. at 195:25-196:8 (agreeing with the conclusion of the Reilly paper that "there is no single plasma concentration range that provides optimal benefit/risk for all patients"); *id.* at 195:21-22 ("[Y]es, it's a true statement for all patients, there's no single range . . . .").

[5] Ex. B, Reilly et al., *The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients*, 63 J. Am. C. Cardiology 321, 328 (2014).

communities remains that there is no optimal range for all patients and that monitoring should not be required.[6]

Finally, Dr. Harvey has never independently tested his monitoring theory. *See id.* at 179:12-180:9, 184:8-16 (stating that he never tried to quantify whether there is a plasma range increase at which there is not increased stroke protection); *see Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 594 (1993) testing "is what distinguishes science from other fields of human inquiry.") (quoting C. Hempel, Philosophy of Natural Science 49 (1966)); *Nease v. Ford Motor Co.*, 848 F.3d 219, 232 (4th Cir. 2017) (excluding expert's testimony where he "presented a hypothesis only -- he failed to validate it with testing"); *Fireman's Fund Ins. Co. v. Tecumseh Prods. Co.* 767 F. Supp. 2d 549, 554-55 (D. Md. 2011) (failure to test "often grounds for excluding expert testimony."). He has never written down or discussed his proposed warnings with other doctors to test if they would understand those warnings. Ex. A, Harvey 11/30/17 Dep. at 280:18-282:5. He has never subjected his views to peer review more broadly -- in fact, he has never published any articles on anticoagulants or stroke. *Id.* at 40:19-41:4. Finally, like all of the other opinions he has offered in this case, Dr. Harvey has never expressed his monitoring views outside of the context of this litigation, and he has no intention of doing so. *Id.* at 42:20-43:6.

In sum, because Dr. Harvey's monitoring opinions lack a reliable methodology, these opinions should be excluded.

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[6] *See* Ex. A, Harvey 11/30/17 Dep. at 195:25-196:8 (agreeing with the conclusion of the Reilly paper that "there is no single plasma concentration range that provides optimal benefit/risk for all patients"); *id.* at 492:12-23 (acknowledging the consensus view expressed in the Reiffel article that monitoring "remains unproven"); *id.* at 233:9-12 (confirming that no regulator in the world

III. Dr. Harvey's "Reasonable Company" Opinions Should Be Excluded.

BI anticipates that Dr. Harvey will also offer testimony at trial that BI's underlying conduct in this case does not comport with what a "reasonable company" would have done under similar circumstances.[7] However, because Dr. Harvey lacks any reliable methodology for offering such "reasonable company" opinions, these opinions should be excluded.

Most problematically, Dr. Harvey has specifically refused to consider the conduct of other pharmaceutical companies that manufacture and market similar NOACs in formulating his opinion as to what BI should have done as a "reasonable company." Dr. Harvey's failure to evaluate or even acknowledge the actions that these other pharmaceutical companies have actually taken (or not taken) in the real world should exclude him from offering any subjective opinion as to what a "reasonable company" might do in the abstract. *Tyger Constr. Co. v. Pensacola Constr. Co.*, 29 F.3d 137, 142 (4th Cir. 1994) ("An expert's opinion should be excluded when it is based on assumptions which are speculative and are not supported by the record.").

Dr. Harvey testified that other manufacturers of NOACs are "reasonable" companies. *See, e.g.*, Ex. A, Harvey 11/30/17 Dep. at 238:8-11 (stating that Pfizer, which markets Eliquis with Bristol-Myers Squibb, "is a reasonable pharmaceutical company"); *id.* at 238:21-22 (stating that Johnson & Johnson, which markets Xarelto with Bayer, is a reasonable company). But despite the fact that similar criticisms have been levied against the other NOACs as the Plaintiffs allege with respect to Pradaxa in this case, Dr. Harvey refused to consider the conduct of other NOAC manufacturers in formulating his opinion as to whether BI's conduct is

[7] *See, e.g.*, Ex. A, Harvey 11/30/17 Dep. at 236:16-20 ("Q. And your testimony as I understand it is that a reasonable company would do more to evaluate and warn about plasma concentration; correct? A. Yes."); Ex. C, Harvey Report at ¶ 245 (noting Dr. Harvey's "opinion that BI has failed to adequately study and investigate its drug product as required by . . . the obligations of what a reasonable drug company would do under these circumstances").

reasonable, instead repeatedly insisting on limiting his opinions to Pradaxa alone. *See id.* at 68:12-21 ("I'm not here to serve as an expert on Eliquis. . . . So I would actually like to just confine my analysis to [Pradaxa] because that was the topic of my report."); *id.* at 237:17-238:3 ("I haven't studied [the other NOAC manufacturers] for my report. . . . My report was confined to BI and what they did."); *id.* at 69:22-23 ("I did not do an in-depth analysis of the other anticoagulants."); *id.* at 67:11-20 (stating that he is not even aware that the same criticisms he makes regarding Pradaxa have been made of other NOACs).

Dr. Harvey's reason for limiting his opinions to Pradaxa and ignoring other NOACs is clear. The fact that BI's actions have been consistent with -- and have often exceeded -- those of other NOAC manufacturers critically undermines Dr. Harvey's opinion that BI did not act as a "reasonable company" should have.[8]

For example, with respect to his plasma monitoring opinions, Dr. Harvey agreed that monitoring criticisms regarding Pradaxa could similarly apply to other NOACs. *See id.* at 236:21-237:2, 67:21-68:4.[9] But despite testifying that the other NOAC manufacturers were reasonable companies, he could not point to any company that has taken steps with respect to investigating monitoring that BI has not taken. *Id.* at 240:15-241:5. Nor could he point to any other company that has taken the same steps that BI *has* taken "in terms of gathering plasma data, analyzing plasma data, reporting it to regulators, and publishing on it." *Id.* at 242:10-20; *see also id.* at 69:16-23, 70:6-10 (stating that he was unaware that, although plasma

[8] Notably, Dr. Harvey was willing to invoke other pharmaceutical companies when doing so was helpful to his opinions. *See, e.g.*, Ex. A, Harvey 11/30/17 Dep. at 165:17-25 (stating that Pfizer and Sanofi utilized Changes Being Effected filings where appropriate).

[9] *See also* Ex. A, Harvey 11/30/17 Dep. at 70:20-72:21 (failing to identify any mechanism of action that would make blood concentration testing appropriate for Pradaxa but not for Xarelto and Eliquis, and testifying that he had "no basis to rule in and rule out" whether such testing should be required for Xarelto or Eliquis).

concentration data was collected for Pradaxa in the RE-LY trial, such plasma concentration data was not collected in the pivotal trials for Eliquis and Xarelto).

Similarly, as to the reversal agent, Dr. Harvey concedes that he is "not aware of any specific efforts" by other NOAC manufacturers to develop reversal agents, and that whatever efforts have been made have not yet resulted in FDA approval. *Id.* at 391:5-14.[10] But when asked whether those other NOACs should be kept off the market for not having a reversal agent, consistent with Dr. Harvey's opinion as to Pradaxa without a reversal agent, Dr. Harvey insisted that this issue was "outside the scope" of his report and that he did not consider other NOACs in forming his opinions. *Id.* at 391:15-20, 393:12-24. However, the fact that BI remains to this day the only company to have successfully developed and secured approval for a NOAC reversal agent is critical to evaluating whether BI acted reasonably with respect to the development of the reversal agent. Dr. Harvey's refusal to acknowledge this fact by limiting his testimony to Pradaxa alone cannot shield his testimony from preclusion on these grounds.

Further compounding the defects in Dr. Harvey's "reasonable company" opinions is the fact that Dr. Harvey may actually be excluded from offering testimony critical of Pfizer or Johnson & Johnson due to his prior employment and ongoing consulting relationships with these companies. Dr. Harvey specifically testified that, due to his non-disparagement agreement with Pfizer following his prior employment by that company, he would need to "check with Pfizer on that and get a legal opinion" before serving as an expert witness in litigation involving Eliquis. *Id.* at 66:6-13, 66:20-67:6. Dr. Harvey further testified that he could not even offer testimony in the instant litigation as to whether criticisms of Pradaxa apply equally to Eliquis before first

[10] In fact, Dr. Harvey could not point to a single example of another company that had developed and secured approval for a product using an antibody to reverse potentially harmful effects of its medicine other than BI with Praxbind. *See* Ex. A, Harvey 11/30/17 Dep. at 389:11-390:7.

"talk[ing] to Pfizer to make sure [he] wasn't violating any agreement." *Id.* at 72:22-73:6. Similarly, given his ongoing consulting relationship with Johnson & Johnson, Dr. Harvey testified that he would "have had to check with them" before giving any expert testimony against that company, such as testimony critical of Xarelto. *See id.* at 118:14-19, 121:16-19. These admitted conflicts of interest relating to other NOAC manufacturers should exclude Dr. Harvey from offering any "reasonable company" opinions in this case. *See id.* at 75:8-23 (conceding that his Pfizer work constitutes a conflict of interest with respect to Pradaxa such that he would need to disclose his Pfizer work if he published an article critical of Pradaxa).

Because Dr. Harvey's "reasonable company" opinions are inherently subjective and methodologically flawed, these opinions should be excluded.

IV. Dr. Harvey's Company Document Opinions Should Be Excluded.

Dr. Harvey also offers opinions on internal BI company documents that were selectively provided to him by Plaintiffs' lawyers. But because Dr. Harvey's opinions were formed in the absence of any meaningful context or analysis of the documents, and because he instead seeks to impermissibly act as a mouthpiece for lawyers, his testimony should be excluded.

Dr. Harvey's expert report and testimony make clear that he intends to testify as an advocate about what BI knew and intended. *See, e.g.*, Ex. C, Harvey Report at ¶ 335 ("BI did not warn or instruct physicians and patients to measure dabigatran plasma concentrations in an effort to maintain a competitive advantage in the marketplace, with doctors and patients, with institutions and with insurance companies/drug formularies."). A defendant's intent or state of mind are not proper topics for expert testimony. *Cisson v. C.R. Bard, Inc.*, 948 F. Supp. 2d 589, 611 (S.D. W. Va. 2013) ("This Court has consistently found that experts in this MDL may not testify about device manufacturers' 'knowledge, state of mind, alleged bad acts, failures to act, and corporate conduct and ethics.'"); *see also, e.g., In re Fosamax Prods. Liab. Litig.* (S.D.N.Y.

2009) 645 F. Supp. 2d 164, 192 (precluding testimony as to "the knowledge, motivations, intent, state of mind, or purposes of" a company and its employees because it "is not a proper subject for expert or even lay testimony"). Inferring BI's motive from selective statements in BI documents improperly invades the province of the jury, and Dr. Harvey should be excluded from doing so. *See Hines v. Wyeth*, No. 2:04-0690, 2011 WL 2680842, at *5 (S.D. W. Va. July 8, 2011) (excluding expert testimony in part because it "merely regurgitates factual information that is better presented directly to the jury rather than through the testimony of an expert witness").

Nor should Dr. Harvey be permitted to misleadingly narrate sound bites from BI documents that have been cherry-picked by Plaintiffs' lawyers. Dr. Harvey conceded that for certain important issues he reviewed only the limited number of "documents [he] was provided to review" by Plaintiffs' lawyers, *see* Ex. A, Harvey 11/30/17 Dep. at 134:12-18, and he did not attempt to conduct his own review of the full universe of documents available, *see id.* at 508:4-16. Moreover, Dr. Harvey's report misleadingly quotes certain BI documents and selectively ignores others that contradict his opinions. *See, e.g.*, *id.* at 397:19-398:4 (discussing that Dr. Harvey's expert report omits the term "confirmed" from the phrase "[BI] *confirmed* [Praxbind] being the highest priority project for the company," to suggest that the Praxbind was not previously a high priority (emphasis added)); *id.* at 150:25-151:6 (discussing that Dr. Harvey quoted a single question and answer from the deposition of Dr. Paul Reilly regarding reversal agent development in his report, without closely studying the rest of Dr. Reilly's testimony on this issue).

Because Dr. Harvey's opinions regarding internal BI documents are not the product of a reliable methodology, they should be excluded.

V. Dr. Harvey's Reversal Agent Opinions Should Be Excluded.

Dr. Harvey should also be excluded from offering subjective and unsupported opinions as to when BI could or should have developed the Pradaxa-specific reversal agent, Praxbind. As

explained in BI's Motion *in Limine* No. 4 to Exclude Evidence, Testimony, or Argument Related to Pradaxa's Initial Lack of a Reversal Agent and Subsequent Approval of a Reversal Agent, evidence about Praxbind is irrelevant to this case, preempted, and unduly prejudicial. Dr. Harvey's opinions on Praxbind should be excluded for the same reasons.

Setting that aside, Dr. Harvey's opinions on Praxbind are also inadmissible because they are not reliable.

Dr. Harvey does not understand the facts of how the reversal agent was developed, and he therefore cannot assist the jury in drawing conclusions as to whether it should have been developed earlier. For example, Dr. Harvey claims in his expert report that "BI identified mouse antibodies to dabigatran in 2002" and that the "antibody that ultimately became Praxbind had [therefore] been 'on the shelf' for nearly six years when it was rediscovered in 2008." Ex. C, Harvey Report at ¶ 246. But this statement reflects a critical misunderstanding of both the science underlying Praxbind's development and the sequence of relevant events. At the beginning of Pradaxa's development in 2002, BI scientists had developed rabbit -- not mouse -- antibodies, but these antibodies were developed for a purpose unrelated to the reversal agent. *See* Ex. D, van Ryn Dep. at 35:4-17. These antibodies did not "ultimately bec[o]me Praxbind," as Dr. Harvey suggests, Ex. C, Harvey Report at ¶ 246; to the contrary, they were not even suitable to be humanized, *see* Ex. D at 35:44-8, 74:4-15. Subsequently, after BI first identified the novel concept of using an antibody fragment to reverse Pradaxa at the end of 2008, BI scientists screened hundreds of additional antibodies to identify those that could be humanized, before formulating in 2009 the mouse antibody fragment that eventually became Praxbind. *See id.* at 51:9-53:8.

When questioned about these discrepancies at his deposition, Dr. Harvey admitted that he did not "remember the details" about which antibodies had been developed in 2002, Ex. A, Harvey 11/30/17 Dep. at 382:14-383:15; he had no reason to disagree with BI counsel that he was wrong about the existence of mouse antibodies in 2002, *id.* at 383:16-21; he did not know why the 2002 antibodies had been created, *id.* at 383:9-21; he did not "remember the details" as to whether Praxbind was humanized from the same antibody species that existed in 2002, *id.* at 387:8-11; and he did not know that BI had looked at multiple other antibody species as part of Praxbind's development, *id.* at 387:12-18.

Dr. Harvey similarly lacks an understanding of many other key facts regarding the reversal agent's development. *See,* Ex. A, Harvey 11/30/17 Dep. at 381:7-382:13 ("Q. Do you know the number of scientists who were working on the reversal agent at any point in time? A. No, I don't. Q. Do you know the amount of money that Boehringer was spending researching the reversal agent at any specific point in time? A. No, I don't. Q. Do you know the amount of patients or animals that were being studied by Boehringer at any specific point in time? A. No, I don't. Q. How many animal studies were conducted on the reversal agent? A. I don't know. Q. When were they conducted? A. I don't know. Q. How many human studies were conducted? A. I don't know. Q. When were they conducted? A. I don't know."). Moreover, despite selectively citing scattered statements from the testimony of Dr. Reilly regarding Praxbind's development, Dr. Harvey admitted that he did not study Dr. Reilly's full testimony on this topic. *Id.* at 149:19-150:3, 150:25-151:6.

Given this striking lack of knowledge regarding Praxbind's development, Dr. Harvey has no basis for offering testimony as to whether the reversal agent should have been developed earlier, nor can he assist the jury in drawing conclusions on this issue.

Dr. Harvey's arbitrary opinion regarding the timeline under which BI could have secured approval of the reversal agent relies solely on his subjective judgment, but subjective opinions such as these offered without any clear methodology or standards do not constitute reliable scientific evidence. Further, when pressed at his deposition, he would not testify that BI should have waited to launch Pradaxa until 2015 when the reversal agent became available. *See id.* at 391:15-394:7. He also disclaimed his opinion that BI could have developed the reversal agent within a year of designating it as a "top priority." *See id.* at 380:10-16 ("Q. Is it really your testimony that had [BI] just applied that intensity in 2009, they could have gotten it approved within a year? . . . Is that your testimony, sir? A. No, that's not my -- that's not accurate."). Finally, like all of the other opinions he has expressed in this case, Dr. Harvey has never expressed his views with respect to BI's development of the reversal agent outside of the context of this litigation, nor does he have any intention of doing so. *Id.* at 42:20-43:6.

Accordingly, Dr. Harvey's reversal agent opinions should be excluded.[11]

VI. Dr. Harvey's Foreign Labeling Opinions Should Be Excluded.

Finally, BI anticipates that Dr. Harvey will testify at trial as to the contents of foreign Pradaxa labeling materials and that he will opine that the same or similar information should have been reflected in the U.S. Pradaxa label. These opinions should be excluded for the reasons stated in BI's Motion *in Limine* No. 3. In addition, because Dr. Harvey is not qualified to offer opinions regarding foreign Pradaxa labeling, and because his opinions on foreign labeling are not based on any reliable methodology, any such opinions should be excluded.

[11] In addition, Dr. Harvey specifically disclaimed any opinion that BI had violated any law or regulation with respect to the timing of its development of the reversal agent. *See* Ex. A, Harvey 11/30/17 Dep. at 90:21-91:9 ("Q. Is it your opinion that Boehringer violated a federal law or regulation in the manner in which it developed the reversal agent? . . . A. No."); *id.* at 86:9-14 (not offering any opinions as to state law). In light of this sworn testimony, Dr. Harvey should be excluded from offering any opinion to the contrary at trial.

First, Dr. Harvey readily concedes that there are different regulatory standards between the U.S. and other countries and that he is not an expert on pharmaceutical regulation outside of the U.S. Ex. A, Harvey 11/30/17 Dep. at 311:2-5, 85:23-86:3; *see also* Ex. C, Harvey Report at ¶ 101 (acknowledging that Dr. Harvey is "not an expert on the regulation of pharmaceuticals by the European Medicines Agency (EMA)"); Ex. A, Harvey 11/30/17 Dep. at 347:11-14 (stating that "my focus was U.S. FDA" -- as opposed to EMA -- "and that's my main area of expertise"). Dr. Harvey is simply not qualified to offer opinions as to the adequacy of foreign Pradaxa labels or BI's communications with foreign regulatory authorities.

Second, Dr. Harvey did not use a proper methodology to form his opinions regarding foreign Pradaxa labeling. Although he purports to offer opinions about the contents of the European label for Pradaxa -- known as the Summary of Product Characteristics, or "SmPC" -- he admits that he did not read the full European label, let alone review all versions of that label. *See id.* at 310:9-11, 318:18-19. Further, because he did not review the European label for guidance as to when monitoring might be useful or anticoagulation testing recommended, *id.* at 312:17-25, 313:14-18, he was unaware that the SmPC recommended such testing only in limited situations, such as when discontinuing treatment for surgery or in cases of suspected overdose, *id.* at 316:11-318:5. Indeed, Dr. Harvey's review of the SmPC was so cursory that he was not even familiar with the term "SmPC," *id.* at 308:22-309:11, despite the fact that this acronym is commonly used both by the European regulatory authority[12] and by BI employees in the

[12] *See, e.g.*, European Medicines Agency, How to Prepare and Review a Summary of Product Characteristics, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000357.jsp; European Commission, A Guideline on Summary of Product Characteristics (SmPC) (Sept. 2009), *available at* https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf.

documents that he purported to review in support of his opinions (as well as by Dr. Harvey in his own report).

Nor did Dr. Harvey review any of the underlying data supporting the European label or the regulatory communications that resulted in certain language being including that label. Dr. Harvey agreed that, before making any determination that information in the SmPC should also be included in the U.S. label, he "would [] want to understand the data that supported it and the reason that it was added to the European label," but he failed to review the underlying data or regulatory interactions with respect to *any* of the language that he claims is contained in the SmPC and should be included in the U.S. label. *See id.* at 322:17-323:18. And although he selectively cherry-picked language that appears in the SmPC but not in the U.S. label to argue the inadequacy of the U.S. label, he admitted to never comparing the labels for information that was included in the U.S. materials but not the European materials. *Id.* at 470:2-8; *see In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) (excluding experts who "selectively chose [their] support from the scientific landscape"); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (holding that expert could not construct reliable methodology by "cherry picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion").

Dr. Harvey's foreign labeling opinions lack a reliable methodology and should be excluded.

CONCLUSION

For these reasons, BI requests that the testimony of Dr. Harvey be excluded.

BY: /s/ Gretchen M. Callas
Thomas J. Hurney, Jr. (WVSB# 1833)
Gretchen M. Callas (WVSB# 7136)
JACKSON KELLY PLLC
500 Lee Street East, Suite 1600
Charleston, WV 25301-3202
PHONE: (304) 340-1346
FAX: (304) 340-1050
Email: thurney@jacksonkelly.com
Email: gcallas@jacksonkelly.com

Eric E. Hudson (*Pro Hac Vice)*
Ben J. Scott (*Pro Hac Vice)*
Butler Snow LLP
6075 Poplar Avenue
Suite 500
Memphis, TN 38119
PHONE: (901) 680-7200
FAX: (901) 680-7201
Email: eric.hudson@butlersnow.com
Email: ben.scott@butlersnow.com

ATTORNEYS FOR DEFENDANT

IN THE UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
HUNTINGTON DIVISION

CLAUDE R. KNIGHT AND CLAUDIA STEVENS, INDIVIDUALLY AND AS PERSONAL REPRESENTATIVES OF THE ESTATE OF BETTY ERELENE KNIGHT, DECEASED	)	
Plaintiffs,	)	Civil Action No. 3:15-cv-06424
v.	)	JURY TRIAL DEMANDED
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.	)	
Defendant.	)	

CERTIFICATE OF SERVICE

I hereby certify that on this 18th day of April 2018, this document was filed and served pursuant to the Court's ECF system, which sent electronic service to all registered participants.

BY: /s/ Gretchen M. Callas
Thomas J. Hurney, Jr. (WVSB# 1833)
Gretchen M. Callas (WVSB# 7136)
JACKSON KELLY PLLC
500 Lee Street East, Suite 1600
Charleston, WV 25301-3202
PHONE: (304) 340-1346
FAX: (304) 340-1050
Email: thurney@jacksonkelly.com
Email: gcallas@jacksonkelly.com